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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/559,013	04/26/2000	Toshiro Ono	L0461/7086(JRV)	1882

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/559,013	ONO ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *76* is/are allowed.

6)☒ Claim(s) *54,56,60,62,64,66 and 133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 137 has been canceled. claims 56, 76 and 133 have been amended. Claims 54, 56, 60, 62, 64, 66, 76 and 133 are pending and under consideration.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54, 60, 62, 64 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 54 is vague and indefinite in the recitation of "(b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code" without reference to the sequence encoded thereby. Amendment of claim 54 to recite "(b) nucleic acid molecules encoding SEQ ID NO:24" would overcome this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56 and 133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 56 is drawn to a fragment of a nucleic acid molecule consisting of a nucleotide sequence of SEQ ID NO:23 of at least 460 nucleotides and full length complements of (a). Claim 133 embodies the fragments of claim 56 wherein the fragment is at least 1000 nucleotides in length.

The specification teaches that fragments of the nucleic acid sequences of the invention are useful as probes, especially those fragments having 300 or more nucleotides (page 19, lines 22-26). The specification teaches that fragments of the invention include "every integer" from at `least 8 nucleotides to at least 1000 nucleotides (page 7, lines 17-21). Thus, the limitation of at least 460 nucleotides is within the contemplation of the scope of fragments. When given the broadest reasonable interpretation, "at least 460 nucleotides" and "at least 1000 nucleotides" encompasses every fragment of at least 460 nucleotides and every fragment of at least 1000 nucleotides of both SEQ ID NO:23 and the complete complement thereof.

The art teaches that not all fragments of a given nucleic acid sequence are useful as a probe. For instance Mei et al (WO02/042485) teach a computer implemented method for selection of probes. In the instant case, a number of probes of at least 460 nucleotide of SEQ ID NO:23 and at least 1000 nucleotides of SEQ ID NO:23 could be selected, however, the claim encompasses each and every fragment of SEQ ID NO:23 or the complement thereof and the specification fails to teach a use for said fragments which were not useful as probes.

The specification teaches that the fragments can be used in antisense therapy (page 19, lines 29-33). However, the specification is not enabling for antisense therapy. Anti-sense therapy also requires uptake of the administered polynucleotide by the target cells. The specification does not provide dosage or data for administering a therapeutically effective dosage of the complementary sequences of SEQ ID NO:23 or fragments thereof to tumor cells which results in the inhibition of growth, reproduction or survival of cancer cells. It is noted that many anti-sense therapies which appear to be promising using transfection in vitro, fail to provide any therapeutic efficacy when administered in vivo. For instance, Tolcher et al (Clinical Cancer Research, 2002, Vol. 8, pp. 2530-2535) teach that the administration of the anti-sense oligonucleotides ISIS 3521 and 5132 did not possess clinically significant single agent anti-tumor activity in patients having hormone-refractory prostate cancer, although said oligonucleotides were active inhuman tumor models (page 2533, second column, first paragraph under the heading "Discussion"); Cripps et al (Clinical Cancer Research. 2002, 8, pp. 2188-2192) teach that the same oligonucleotides evoked no clinical response in patients having metastatic colorectal cancer. Cripps et al note that although the steady state plasma levels for both oligonucleotide were above the IC50 for inhibition of mRNA expression, these levels may

not have been achieved in the target tissue. Cripps et al also contemplate that additional reasons for the lack of efficacy can be that the target RNA was not important for the particular malignancy or that other unknown intracellular event prevented the drugs from effectively inhibiting protein production (page 2191, column 1, bridging paragraph. These reference serve to demonstrate that there is no absolute nexus between the inhibition of tumor cells by administration of anti-sense oligonucleotide in a tumor model or in vitro, with the administration of anti-sense oligonucleotides to a patient with a tumor. The specification fails to address the effect of the anti-sense compound on tumor cell in vitro, therefore it would be a burden placed upon applicant to first attempt to ascertain if the mRNA was important to the cancerous phenotype of the cell as questioned by Cripps et al (ibid). It is concluded that anti-sense therapy is immature and therefore unreliable. Therefore one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed fragments for anti-sense therapy.

The specification teaches that fragments of the nucleic acid of the invention can be used to produce antibodies (page 19, lines 26-30). It is well known in the art that the prediction of protein fragments that will be immunogenic towards the full length protein is unpredictable and that the smaller fragments encompassed by the claims will not predictably be immunogenic. In particular as drawn to antibodies/binding molecules produced against immunogenic fragments, Clark (Protein engineering of Antibody Molecules for Prophylactic and Therapeutic applications in Man, 1993, pages 4-5) teaches that although it is possible to produce antibodies to almost any part of an antigen, this does not normally happen in an immune response. It is usually found that only a certain areas of the antigen are particularly antigenic, and that a majority of antibodies bind to these regions. These regions are often at exposed areas on the outside of the antigen, particularly where there are loops of polypeptide that lack a rigid tertiary structure (Paul, Fundamental Immunology, 1993, page 249, second column). Furthermore, the peptide fragments do not take into account the 3 dimensional folding of the native molecule, nor its glycosylation or other post-translational modifications and other characteristics which are of significant importance in an antibody response. The instant claims encompass all and every fragment of SEQ ID NO:23 and therefore a use of all and every fragment encoded therefrom must be taught by the specification. Given the teachings in the art regarding the limitations for

generating an antibody which binds to the full length protein using fragments of the encoded protein, one of skill in the art would be subject to undue experimentation in order to use all the fragments of SEQ ID NO:23 of at least 460 nucleotides which encode a fragment of SEQ ID NO:24 to make an antibody which binds to SEQ ID NO:24

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to use all the fragments of SEQ ID NO:23 of at least 460 nucleotides, all the fragments of SEQ ID NO:23 of at least 1000 nucleotides and full length complements thereof with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to use the claimed fragments.

Claim 76 is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643